

The Future of Fluorides and Other Protective Agents in Erosion Prevention

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Key Words

Arginine · Casein · Chitosan · Erosive tooth wear · Fluoride · Mucin · Prevention · Salivary pellicle · Sodium hexametaphosphate · Stannous fluoride · Titanium tetrafluoride

Abstract

The effectiveness of fluoride in caries prevention has been convincingly proven. In recent years, researchers have investigated the preventive effects of different fluoride formulations on erosive tooth wear with positive results, but their action on caries and erosion prevention must be based on different requirements, because there is no sheltered area in the erosive process as there is in the subsurface carious lesions. Thus, any protective mechanism from fluoride concerning erosion is limited to the surface or the near surface layer of enamel. However, reports on other protective agents show superior preventive results. The mechanism of action of tin-containing products is related to tin deposition onto the tooth surface, as well as the incorporation of tin into the near-surface layer of enamel. These tin-rich deposits are less susceptible to dissolution and may result in enhanced protection of the underlying tooth. Titanium tetrafluoride forms a protective layer on the tooth surface. It is believed that this layer is made up of hydrated hydrogen titanium phosphate. Products containing phosphates and/or proteins may adsorb either to the pellicle, rendering it more protective

against demineralization, or directly to the dental hard tissue, probably competing with H^+ at specific sites on the tooth surface. Other substances may further enhance precipitation of calcium phosphates on the enamel surface, protecting it from additional acid impacts. Hence, the future of fluoride alone in erosion prevention looks grim, but the combination of fluoride with protective agents, such as polyvalent metal ions and some polymers, has much brighter prospects.

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For many years, dental erosion was of little interest to clinical practitioners or dental researchers, but recent knowledge and awareness of this condition and its causes have steadily increased [Lussi and Carvalho, 2014]. Likewise, the high prevalence of this condition may reflect the changes in its perception. It could also be related to changing lifestyles, which have involved an increase in the total amount and frequency of consumption of acidic foods and drinks.

Soft drink consumption in the USA increased by 300% [Cavadini et al., 2000] from the 1960s to the 1990s. Between 2003 and 2009, soft drink consumption also increased in other countries, but despite a slight decrease in consumption in places like Germany, Italy, Portugal and Sweden, general soft drink consumption is still high. Energy drink consumption is also high among adolescents,

and, remarkably, 19% of children aged between 6 and 10 years, and even 2% of preschool children (aged 3–5 years), have consumed energy drinks [Zucconi et al., 2013]. This is striking, considering that 4 or more servings per day may be associated with the presence and progression of erosion when other factors are present [Lussi and Schaffner, 2000; O’Sullivan and Curzon, 2000]. It is therefore essential to institute and encourage drastic and durable preventive measures to promote and maintain oral health. In this light, the present review explains how the acidic substances interact with the dental hard tissues, and we then discuss the role of fluoride and other protective agents in erosion prevention.

Dental Hard Tissue and Its Interactions with Surrounding Solutions

Dental hard tissue consists of highly mineralized enamel, as well as dentine and cementum, which contain a much greater proportion of organic matrix. The crystals consist of a calcium-deficient, carbonate-rich hydroxyapatite with a Ca/P ratio of 1.61 instead of 1.66, as for hydroxyapatite. A simplified formula for the tooth mineral is $\text{Ca}_{10-x}\text{Na}_x(\text{PO}_4)_{6-y}(\text{CO}_3)_z(\text{OH})_{2-u}\text{F}_u$; this is different from that of hydroxyapatite, which has the perfect formula $\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$ [Featherstone et al., 1983; LeGeros, 1991].

When there are sufficient Ca^{2+} , PO_4^{3-} , OH^- and F^- ions in the immediate vicinity of the crystals, an equilibrium with the surrounding fluid is established. The activities (i.e. active concentrations) of these ions determine the degree of saturation of the solution. This, in turn, determines whether the tooth mineral will dissolve (‘undersaturation’) or whether mineral deposits will form from the surrounding fluid onto the enamel (‘supersaturation’). During an acid attack, H^+ ions are released from the acid and adhere to different sites on the surface of the dental hard tissues. Further, the PO_4^{3-} and OH^- ion concentrations decrease in solution at lower pHs. These ions then dissolve out of the tooth in order to maintain the solution’s equilibrium in the vicinity of the surface. Hence, these processes depend not only on the solubility of the crystals that make up the tooth surface, but also on the liquid surrounding the tooth [Lussi et al., 2012a; Shellis et al., 2014]. Food and beverages with an erosive potential have no or only minute quantities of calcium or phosphate, so they are undersaturated with respect to dental hard tissue. This implies that undersaturated solutions will dissolve the tooth mineral. However, the rate of

dissolution cannot be estimated solely from the ionic composition of the acidic solution, because other physicochemical factors are of great importance [for a review, see Shellis et al., 2014].

One major factor related to the rate of demineralization is the pH of the solution. The *critical* pH is the pH at which a solution is just saturated with respect to the mineral. If the pH of the solution adjacent to the tooth mineral is above this critical pH, then the solution is considered to be supersaturated with respect to the solid, and no dissolution will occur. In fact, it is more likely that more minerals will precipitate onto the surface of the solid. By contrast, if a solution has a pH below the critical pH value, the solution is considered undersaturated with respect to the solid, and it is capable of causing dissolution of this solid [Dawes, 2003]. In general, at a specific pH, the activities of calcium, phosphate, and to a lesser extent fluoride, will determine the degree of saturation in the solution or fluid with respect to the tooth mineral. In other words, this is the driving force for mineral dissolution. Table 1 gives an overview of various substances, presenting their native pH, mineral content and their critical pH at which these substances are just saturated with respect to hydroxyapatite [Lussi et al., 2012b; Lussi and Carvalho, 2014]. Some products presented no measurable [P], so, to calculate the critical pH of these products, a concentration of 0.01 mM was assumed. This assumption seems to be justified, because in the initial dissolution process some phosphate from dental hard tissue will be released. Additionally, different products contain different organic acids of unknown concentrations. In this case, the critical pH was also calculated as if these acid concentrations were zero. Although some (marginal) error originated from these assumptions, the values presented in table 1 provide a good general view of the potential clinically erosive effect of the different products. In other words, if the pH of the products is lower than the critical pH, the product will cause (to some extent) erosion, whereas if the pH is higher than the critical pH, the product will be non-erosive [R.P. Shellis, pers. commun.].

When surface demineralization occurs, because the liquid surrounding the enamel mineral is undersaturated with respect to the crystals, a local rise in pH will tend to occur thereafter. This is due to the increased concentrations of ions that are released from the enamel crystals and dissolved in the liquid layer adjacent to the enamel. Consequently, this semi-static layer (the ‘Nernst layer’) close to the enamel surface becomes approximately saturated, and demineralization of the underlying crystals will slow down considerably. However, an increase in agitation (e.g.

Table 1. pH, calcium and phosphate concentrations of different beverages and foodstuffs and the calculated critical pH (pH_c) with respect to hydroxyapatite (from Lussi et al. [2012b] and unpublished data)

Agents tested	pH	[Ca], mM	[P], mM	pH _c	Agents tested	pH	[Ca], mM	[P], mM	pH _c
Soft drinks					Medication				
Carpe Diem Kombucha fresh	3.0	3.3	0.1	5.6	Alca-C fizzy tablet	4.2	9.0	0.0	5.6
Coca Cola	2.5	1.1	5.0	5.1	Alcacyl 500	6.9	1.9	0.0	6.1
Coca Cola light	2.6	0.8	4.9	5.2	Alka-Seltzer fizzy tablet	6.2	2.1	0.0	5.9
Fanta regular	2.7	0.5	0.1	6.1	Aspirine-C fizzy tablet	5.5	2.0	0.0	6.1
Ice tea classic	2.9	0.5	0.1	6.2	Fluimucil 200 fizzy tablet	4.7	2.0	0.0	6.1
Ice tea lemon	3.0	0.2	0.1	6.3	Neocitran	2.9	4.6	1.6	4.9
Ice tea peach	2.9	0.1	0.2	6.4	Siccoral	5.4	0.2	0.1	6.3
Pepsi Cola	2.4	0.3	4.9	5.5	Vitamin C fizzy tablet 1	3.9	1.9	0.0	5.9
Pepsi Cola light	2.8	0.3	4.7	5.5	Vitamin C fizzy tablet 2	3.6	1.8	2.0	5.1
Rivella blue	3.3	4.0	2.2	4.9	Yoghurt, milk				
Rivella green	3.2	3.3	2.4	4.9	Forest berries	3.8	45.5	36.8	3.9
Rivella red	3.3	3.1	2.3	4.9	Kiwi Tropicana	4.0	45.8	33.8	3.9
Sinalco	3.1	1.1	0.1	5.8	Lemon	4.1	32.0	39.9	3.9
Sprite	2.5	0.3	0.0	6.5	Natural	3.9	43.3	34.3	3.9
Sprite zero	3.0	0.3	0.0	6.6	Slimline	4.0	56.3	38.7	3.8
Sports and energy drinks					Milk	7.0	29.5	18.9	4.1
Gatorade	3.2	0.1	3.0	5.8	Sour milk	4.2	69.0	39.2	3.8
Isostar	3.9	8.2	4.5	4.6	Mineral water				
Powerade	3.7	0.3	0.0	6.6	Henniez	7.7	2.5	0.0	6.0
Red Bull	3.3	1.9	0.0	6.1	Henniez sparkling	6.1	2.4	0.0	6.0
Fruit juice and fruits					Valser	5.6	9.9	0.0	5.7
Apple juice	3.4	2.0	1.7	5.1	Valser Viva Lemon	3.3	9.8	0.1	5.3
Carrot juice	4.2	4.4	1.2	5.0	Tea and coffee				
Grapefruit juice	3.2	2.3	2.2	5.0	Black tea	6.6	1.1	0.3	5.6
Multivitamin juice	3.6	4.8	6.5	4.7	Peppermint	7.5	1.9	0.4	5.4
Orange juice 1	3.7	2.4	2.4	5.0	Rose hip	3.2	2.7	0.4	5.3
Orange juice 2	3.6	2.0	2.6	5.0	Wild berries	6.8	1.1	0.2	5.6
Pineapple juice	3.4	1.7	1.9	5.1	Espresso	5.8	0.7	0.6	5.6
Apricot	3.3	1.2	6.0	5.1	Salad dressing				
Kiwi	3.3	3.4	4.5	4.8	Thomy French Classic	4.0	20.5	0.5	4.8
Orange	3.6	2.2	1.3	5.2	Thomy French Light	3.9	40.0	1.1	4.5
Alcoholic drinks					pH _c values were calculated by R.P. Shellis (Department of Preventive, Restorative and Pediatric Dentistry, University of Bern, Switzerland).				
Bacardi Breezer	3.2	0.2	0.1	6.2					
Champagne	3.0	1.9	2.0	5.1					
Red wine 1	3.4	1.3	4.7	5.1					
Red wine 2	3.7	1.7	2.8	5.1					
Smirnoff vodka	3.1	0.2	6.5	5.6					
White wine	3.6	1.3	4.4	5.1					

when a person swishes the drink in his or her mouth) will enhance the dissolution process. The ions in the solution layer adjacent to tooth mineral will therefore be constantly exchanged, and no saturation level will be reached [Lussi et al., 2011; Shellis et al., 2014]. In other words, the Nernst layer will remain undersaturated with respect to the tooth mineral and dissolution will continue, leaving a small decalcified and softened layer of dental hard tissue – of a few micrometres in depth – which will be formed

by the action of the acids [Lussi et al., 2011]. Shellis et al. [2013] were able to prove experimentally that erosive dissolution occurs not only at the interface between solution and enamel, but also within the thin, partly demineralized softened enamel layer. For this process, they suggested the term ‘near-surface demineralization’. It describes the softening process during dental erosion, emphasizing the fact that dental erosion is not exclusively a surface phenomenon, but it also occurs within the limited extent of the soft-

ened layer due to the effect of the undissociated form of the organic acids [Featherstone and Rodgers, 1981; Shellis et al., 2013]. These undissociated acids may diffuse into the demineralized layer and, once they reach the adjacent underlying tissue, the molecules will dissociate, releasing H^+ ions that will then dissolve the mineral. The authors concluded that this process depends primarily on the concentration of the undissociated form of the organic acids within the enamel pores, rather than on the buffering properties of the acid itself [for a review, see Lussi and Carvalho, 2014; Shellis et al., 2014].

Dissolution of crystals takes place at specific sites on the surface of the tooth. Inhibitory substances can adsorb to the solid surface and hinder the exchange with the surrounding solution. In order to block these specific dissolution/growth sites on the tooth surface, the concentration of adsorbed inhibitor required to interfere with these processes does not need to be high [Stumm, 1992]. Inhibitor molecules with a high affinity for these sites could have some potential in the future for prevention against erosive demineralization.

Some natural and healthy inhibitors could be added to erosive beverages or foodstuff in order to reduce their erosive potential. These processes are enhanced at higher concentrations of the inhibitors, but there are some limitations if tooth surfaces are modified with saliva and the pellicle, which can interfere with the effective coverage of these sites. One example of the mechanism of these inhibitors is the addition of calcium to erosive solutions in the form of $CaCO_3$. Adding calcium to erosive solutions will not only increase the pH of the solution, but it will also increase the level of saturation of the solution [Shellis et al., 2014]. Both these mechanisms will lower the erosive potential of the solution [Venables et al., 2005].

Other compounds will also act directly on the enamel surface, increasing its ability to withstand demineralization, and, thus, exhibit erosion prevention properties. We now turn our discussion to the mode of action of fluoride and various other protective agents in erosion prevention.

Mode of Action of Fluoride in Erosion Prevention

In human enamel, less than 5% of the OH^- sites of hydroxyapatite are replaced by fluoride [Weatherell et al., 1977]. Incorporation of such a small amount of fluoride into the mineral components of enamel reduces the solubility to a limited extent. However, small quantities of fluoride in the solution surrounding the tooth will inhibit demineralization more effectively than the above-men-

tioned amount of incorporated fluoride [ten Cate and Duijsters, 1983a, b]. Fluoride ions are, in part, adsorbed onto the crystalline surface and maintain a dynamic equilibrium with the fluoride ions in the solution present in the immediate vicinity of the tooth. The adsorption of fluoride leads to partial conversion of the crystal surface to fluor(hydroxy)apatite and hence reduces the solubility of the surface. Thus, the adsorption of fluoride on the crystals is thought to offer direct protection from demineralization [for a review, see Lussi et al., 2012a]. The presence of fluoride in the solution between the crystals is also likely to encourage precipitation of fluor(hydroxy)apatite and hence remineralization.

On the other hand, calcium fluoride, or calcium fluoride-like (CaF_2 -like) material to be more precise, is considered an important factor for caries prevention, and it precipitates on the tooth's surface when compounds containing F^- are applied. The lower the pH of the solution, and the longer the application time, the more material precipitates. The calcium ions relevant for the formation of CaF_2 -like material originate either from saliva or, in part, from the tooth when slightly acidic fluoride solutions are applied [Saxegaard and Rolla, 1989; Larsen and Richards, 2001]. These CaF_2 -like deposits increase the F^- content of plaque for several hours, so reduced changes in surface microhardness and hence some protective capability against caries has been shown [Tenuta et al., 2008]. However, their influence on the prevention of dental erosion has not been shown conclusively. In order to protect the tooth surface completely, the CaF_2 -like layer should be dense enough to build up a physical barrier that protects the underlying enamel from acid impacts and it should be stable enough against erosive dissolution. Even though CaF_2 is stabilized *in vivo* due to adsorption of hydrogen phosphate ions (HPO_4^{2-}) and proteins onto the surface of the CaF_2 crystals, CaF_2 will not fully protect the underlying tissue. The application of fluoride varnishes showed an increase in fluoride contents on the enamel surface, but this increase was not able to prevent enamel erosion [Carvalho et al., 2014]. Similarly, even under optimized conditions for CaF_2 -like precipitation, with fluoride concentration similar to that of toothpastes, no more than 40% of enamel surface coverage can be achieved [Koeser et al., 2014]. This is observed in figure 1. Hence, CaF_2 particles function mostly as a pH-driven F^- reservoir, releasing F^- at low pH during an acid attack and remaining relatively stable on the enamel surface at neutral pH [Rölla and Ekstrand, 1996]. Therefore, applying fluoride formulations with the sole purpose of enhancing the formation of CaF_2 -like deposits to prevent dental erosion

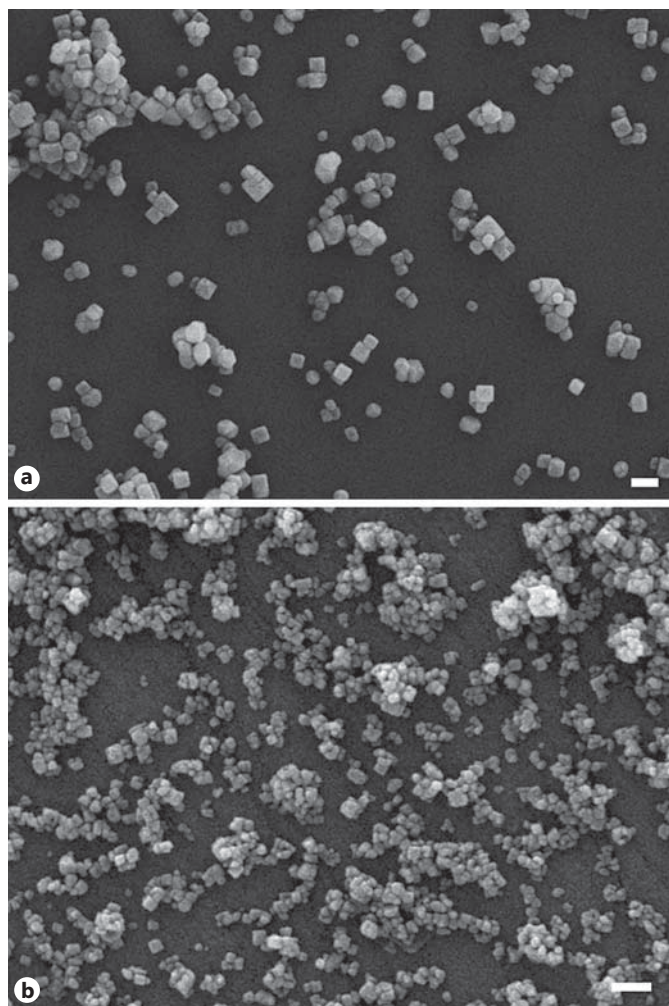


Fig. 1. Scanning electron microscopy images of CaF_2 particles on enamel surface after using a solution with the fluoride concentration corresponding to that of dentifrices (1,450 ppm). The typical size of the CaF_2 particles is <200 nm (**a**). Note that the enamel surface is not entirely covered with a CaF_2 layer (**b**). Scale bars: **a** 200 nm, **b** 500 nm. Pictures from Joachin Köser (Department of Preventive, Restorative and Pediatric Dentistry, University of Bern, Switzerland; Fachhochschule Nordwestschweiz, Hochschule für Life Sciences, Institut für Chemie und Bioanalytik).

will provide only a limited protective potential against erosion.

In relation to dental caries, the formation of the CaF_2 -like material is closely related to the mineralization process, where the demineralized crystals may serve as nuclei for mineral precipitation and fluoride accelerates this process, resulting in a fluoride-rich, carbonate-poor mineral [Featherstone, 2000]. This is a slow process that only occurs in an optimum 'protected' area within the shel-

tered subsurface lesion. This mineralization process is different in erosive lesions. In the latter, there is no 'sheltered area', so any mineralization process is limited to the surface and near-surface layers of enamel, and it is restricted to the softened (demineralized) enamel layer.

Mode of Action of Other Protective Agents in Erosion Prevention

Most fluoridated products show only a slight preventive effect against erosion, and the best results are observed when compared to non-fluoridated (placebo) products. Recent research has therefore focused on other protective agents, namely those containing polyvalent metal ions (tin or titanium), or products with added amino acids, peptides or proteins.

Polyvalent Metal Ions

Products Containing Tin Ions

The effect of dental products containing polyvalent metal ions has been widely studied in dentistry. Products containing tin ions, for example, have long been known to provide good protection against demineralization [Rølla and Ellingsen, 1994]. The mode of action of such products is mostly based on the reaction between the tin ions and the dental hard tissue, to form Sn_2OHPO_4 , $\text{Sn}_3\text{F}_3\text{PO}_4$, and $\text{Ca}(\text{SnF}_3)_2$ salts [Babcock et al., 1978]. These salts form a stabler layer that is resistant to acidic dissolution [Hove et al., 2006]. Schlueter et al. [2009a] observed a layer of approximately 500 nm formed on the surface of enamel exposed to tin- and fluoride-containing solutions.

The tin-rich layer forms on both eroded and non-eroded enamel surfaces. On non-eroded enamel, the layer is limited to the surface, and it seems to be relative to the concentration of tin in the solution surrounding the tooth mineral, but also restricted by saturation principles. Interestingly, on eroded enamel, though regulated by an equivalent saturation mechanism, the presence of tin was observed up to a depth of 20 μm in the enamel mineral [Schlueter et al., 2009a]. Therefore, it is currently accepted that the mechanism of action of tin-containing products on eroded enamel is related to tin deposition onto the tooth surface, as well as the eventual incorporation of tin into the near-surface layer of enamel. These tin-rich deposits are less susceptible to dissolution, they are enhanced by repetitive applications and eventually result in

enhanced protection of the underlying tooth with considerably less surface loss after further acid impacts [Khambe et al., 2014].

It is already known that fluoride can have some limited protective effect against erosive mineral loss. Interestingly, tin alone was able to cause a similar reduction in mineral loss as fluoride [Ganss et al., 2008], but when both tin and fluoride were present in a solution together (either as SnF_2 or as AmF/SnCl_2), the inhibition of mineral loss was significantly more efficient [Schlueter et al., 2009b, 2010].

Several in situ studies have been carried out analysing the mode of action and preventive effect of tin-containing solutions and dentifrices, and the vast majority show positive results. When testing dentifrices, Ganss et al. [2004] observed that the use of a tin-containing dentifrice significantly reduced enamel mineral loss in relation to the negative control group (no fluoridation). Huysmans et al. [2011] observed that tin-containing dentifrices yielded significantly better results than the sodium fluoride dentifrice, significantly reducing tooth wear by over 20%. In another study, Hooper et al. [2014] showed that a tin-containing dentifrice led to a 25% reduction in enamel surface loss after 5 days of application, and a 38% reduction after 15 days, when compared to a sodium fluoride dentifrice. Hystad Hove et al. [2014] also showed that a tin-containing dentifrice reduced enamel wear in comparison to the negative control group (no fluoridation). Similarly, Bellamy et al. [2014] observed that treatment with the tin-containing dentifrice resulted in more than 85% less surface loss than the negative control (no fluoridation). And when comparing the effect of exposure to dentifrice slurry (erosion-only) or slurry together with toothbrushing (erosion-abrasion), Schlueter et al. [2013] showed that the tin-containing dentifrice had a significantly better efficacy in both experimental models, resulting in a reduction in enamel loss of more than 50%.

Dentifrices containing stannous fluoride (SnF_2) together with sodium hexametaphosphate have also been tested in situ. When comparing them to a sodium fluoride dentifrice, Hooper et al. [2007] observed that the dentifrice containing SnF_2 and sodium hexametaphosphate exhibited less enamel surface loss than a sodium fluoride (tin-free) control dentifrice. Besides the beneficial effect of the stannous ions, hexametaphosphates can be incorporated into salivary pellicle [Busscher et al., 2002] or into the protective layer formed on the enamel surface; this is because the phosphate groups in the hexametaphosphate polymer can bind to free calcium sites on the enamel surface [Hooper et al., 2007]. Still, different results have been found with dentifrices containing SnF_2 and sodium

hexametaphosphate [Barlow et al., 2009], so further experiments are still necessary.

In regard to rinse solutions containing tin, several studies have reported positive results in situ [Schlueter et al., 2009c; Ganss et al., 2010; Schlueter et al., 2011]. The tin-containing rinse was able to significantly reduce enamel surface loss by 73% [Schlueter et al., 2009c], 65% [Schlueter et al., 2011] or 67% [Ganss et al., 2010] in comparison to a negative control group, whereas a NaF rinse resulted only in a 19% reduction [Ganss et al., 2010]. However, when previously eroded enamel was intra-orally exposed to tin-containing rinse or to a casein phosphopeptide-stabilized amorphous calcium phosphate (CPP-ACP) mousse, neither product showed a beneficial effect on enamel rehardening [Wegehaupt et al., 2012]. On the basis of these slightly contradictory results, one may speculate that the main effect of the tin-containing rinse is related to hindering further enamel surface loss rather than an effect on the actual rehardening of the demineralized (softened) enamel. Moreover, it is important to bear in mind that any remineralization occurs at a slow rate [Garberoglio and Cozzani, 1979].

Likewise, the mode of action of dentifrices is also related to hindering enamel loss rather than remineralizing the enamel surface. Carvalho and Lussi [2014] showed that after dentifrices had been used on eroded enamel, surface microhardness increased, and this increase in hardness was clearly a result of the partial removal of the softened (eroded) enamel layer, and not a remineralization of the enamel per se. On the other hand, the authors also showed that the tin-containing dentifrice hindered further enamel softening after subsequent erosive challenges. So, the general mechanism of action of tin-containing products in erosion protection is to inhibit further near-surface demineralization (enamel softening) and not to remineralize the eroded enamel.

Products Containing Titanium Ions

Similar to tin-containing products, solutions and varnishes based on titanium tetrafluoride (TiF_4) form a protective layer on the tooth surface. It is believed that the glaze-like surface layer is made up of hydrated hydrogen titanium phosphate, which forms when TiF_4 reacts with the tooth mineral [Magalhães et al., 2011]. Several in vitro studies have noted the beneficial effects of TiF_4 , but the number of clinical (in situ) trials is limited, and they report conflicting results. In an in situ erosion-only model, Magalhães et al. [2009] observed that the application of a 4% TiF_4 solution (1.29 mol/l F; pH 1.2) significantly reduced enamel hardness loss after erosive demineraliza-

tion. Wiegand et al. [2010a] also assessed a TiF_4 solution ($1.55\% = 0.5 \text{ mol/l F}$; pH 1.7) and compared it to other fluorides (ZrF_4 , HfF_4 or AmF , all 0.5 mol/l F) in an erosion-only or erosion-abrasion model. The authors observed that all fluoride solutions were able to reduce enamel loss in relation to the control group (no fluoridation) in both experimental models, but no differences were found between the TiF_4 solution and the positive control (AmF ; 0.5 mol/l F) group. Magalhães et al. [2008] carried out an erosion-only in situ trial with a 4% TiF_4 solution (1.29 mol/l F ; pH 1.2) compared to a non-fluoridated control. Although the authors clearly observed the formation of a layer on the enamel surface after the use of TiF_4 solution, they concluded that the solution was not able to prevent erosion.

Some in situ [Hove et al., 2008; Stenhagen et al., 2013] and in vivo [Hjortsjo et al., 2009] studies have compared both TiF_4 and tin-containing products. Hove et al. [2008] tested different fluoride solutions (1.5% TiF_4 ; 3.9% SnF_2 ; 2.1% NaF ; all solutions contained 0.5 mol/l F) in an in situ erosion-only model and found that the TiF_4 and the SnF_2 both formed a protective surface layer on enamel, and both showed significant protection against erosion in comparison to the NaF solution and to placebo (no fluoride treatment); however, the authors did not observe any significant differences between TiF_4 and SnF_2 . Similarly, in the in situ erosion-abrasion study by Stenhagen et al. [2013], the protective layer on enamel had an average thickness of $0.6 \mu\text{m}$ for TiF_4 and of $1.0 \mu\text{m}$ for SnF_2 , and the TiF_4 and SnF_2 solutions led to a reduction in enamel erosive-abrasive wear of 90 and 94%, respectively. The authors also reported no significant differences between the protective effect of TiF_4 and SnF_2 solutions. Contradictory results were obtained when NaF (pH 7.3), SnF_2 (pH 2.9) and TiF_4 (pH 1.5) solutions [Hjortsjo et al., 2009] of similar fluoride concentrations ($\approx 0.1 \text{ mol/l}$) were tested. In this in vivo study, front teeth of patients were isolated, eroded with citric acid (5 ml; 0.1 mol/l ; pH 2.7, which was allowed to drip over the tooth surface at a rate of 6 ml/min), and then they were exposed to the test solution for 1 min. The erosive challenge was later repeated and the amount of calcium was measured in the acid after each erosive challenge. The authors observed that the treatment with SnF_2 solution significantly reduced subsequent calcium dissolution from enamel, but neither NaF nor TiF_4 solutions were able to reduce calcium release [Hjortsjo et al., 2009].

These conflicting results might be explained by differences in experimental protocols, fluoride concentrations or pH of the solutions. The pH is of particular importance because most TiF_4 products have a very low native pH,

with values ranging between pH 1 and pH 2. Such a low pH is a major drawback for TiF_4 products, mainly because of the potential adverse effects on hard and soft tissues, limiting the possible home use of the product and its self-application by patients [Wiegand et al., 2010b; Huysmans et al., 2014]. In any case, simply increasing the pH of TiF_4 solutions is not a viable option at present. The reduction in enamel erosion is primarily due to the formation of the glaze-like protective layer, which, in turn, is highly dependent on the low pH of the TiF_4 solution [Wiegand et al., 2009].

Amino Acids, Peptides, Proteins or Polymers

Products Containing Arginine

Arginine is a semi-essential amino acid, and when added to toothpaste (concentration of 1.5%), it has complementary actions with calcium carbonate and fluoride [Cummins, 2013]. It may act directly on plaque biofilm, maintaining plaque slightly supersaturated with respect to the tooth mineral [Souza et al., 2013; Srisilapanan et al., 2013], but dental erosion occurs in the absence of plaque. In vitro studies on erosion showed the formation of a calcium-rich layer over demineralized enamel [Rege et al., 2014], where it is thought that arginine modifies the surface charge of enamel, heightening the affinity of calcium carbonate for the tooth surface [Rege et al., 2014]. However, this calcium carbonate layer is very soluble and too short-lived to cause considerable effects on mineral precipitation. Also the effect of monofluorophosphate (MFP) from the toothpaste will be strictly dependent on the presence of phosphatases in the oral cavity, since MFP hydrolysis was shown to be significantly greater in patients with large amounts of plaque [Klimek et al., 1997].

In situ studies with arginine [Sullivan et al., 2014a, b] showed that, in comparison to a positive control dentifrice (1,450 ppm F as MFP), previously eroded enamel samples presented a 15% increase in surface microhardness, compared to 9% increase from the positive control (MFP) dentifrice [Sullivan et al., 2014b]. In a cyclic erosion-only model arginine-containing dentifrice caused a significantly lower mineral loss ($10 \pm 13\%$) than the positive control (MFP) dentifrice ($18 \pm 14\%$) [Sullivan et al., 2014a]. However, not enough research has been published in order to draw full conclusions on the role of arginine in the prevention of erosive tooth wear, so it is important to emphasize the necessity for further studies on this topic. In dentine hypersensitivity, which is a common condition associated with erosive tooth wear [West et al., 2013], the

build-up of calcium phosphate precipitates leads to the formation of plugs, resulting in the occlusion of the dentine tubules [for a review, see West et al., 2014].

Products Containing CCP-ACP

CPP-ACP is derived from the milk protein casein. Several reviews discussed researches on CPP-ACP [Cochrane et al., 2010; Cochrane and Reynolds, 2012; Nongonierma and Fitzgerald, 2012; Buzalaf et al., 2014], but most are related to dental caries. CPP-ACP stabilizes calcium and phosphate ions in a similar manner to statherin and proline-rich proteins. The calcium and phosphate ions are released from the CPP-ACP complex, increasing the activity of these ions on the enamel surface. So, when fluoride is present, the formation of CaF_2 -like particles is increased due to the presence of more Ca^{2+} on the tooth surface. This mode of action is favourable in plaque-covered enamel or within subsurface caries lesions, where the environment is 'protected', but here again, dental erosion occurs in the absence of plaque, thus the results of the role of CPP-ACP erosion prevention remain contradictory.

Erosion studies using in situ models showed that eroded enamel exhibited a greater increase in microhardness (30–96%) when chewing gum containing CPP-ACP was used, in comparison to when chewing gum without CPP-ACP was used [Prestes et al., 2013; de Alencar et al., 2014]. The effect of CPP-ACP paste provided an increase in microhardness of 46% when the paste did not contain fluoride, but the presence of 900 ppm F in the paste caused a 64% increase [Srinivasan et al., 2010]. Comparing CPP-ACP paste (with and without 900 ppm F) with milk (with and without 5 ppm F), neither CPP-ACP nor the milk were able to reduce enamel surface loss, but fluoridated dentifrice as well as a tin-containing rinse induced enamel protection [Wiegand and Attin, 2014]. CPP-ACP crème applied intra-orally on previously eroded enamel presented no benefit on enamel rehardening either [Weghaupt et al., 2012]. It may be possible that chewing gum or application of the paste can partly remove the softened enamel layer, leading to a slight increase in surface hardness. This could account, at least in part, for the different results observed in the aforementioned studies.

These conflicting results can be explained by the histological nature of dental erosion and the relative shorter retention time on the paste in case of erosion [Wang et al., 2011]. Bearing in mind that remineralization is a slow process, it is hypothesized that, since dental erosion occurs in the absence of plaque and the tooth surface is essentially exposed to further (subsequent) acid impacts, it

is highly likely that if (any) remineralization is to derive from CPP-ACP it will not be particularly advanced by the time of the next acid impact. This would imply that the presence of calcium and phosphate on the tooth surface is probably short-lived, and enamel is deprived of any clinically relevant remineralization time. Nevertheless, in view of the conflicting results, we emphasize the need for further in situ/in vivo research, in order to establish full conclusions on the role of CPP-ACP on the prevention of erosive tooth wear.

Products Containing Other Proteins or Polymers

Different proteins can directly interact and modify the acquired enamel pellicle (AEP) [Vukosavljevic et al., 2014]. The AEP is a protein-rich film covering the surfaces of the teeth, formed as a result of the selective adsorption of salivary proteins to the dental enamel [Siqueira et al., 2012], and plays a significant role in protection against erosive challenges [Hara et al., 2006; Hannig and Hannig, 2014]. The vast majority of in situ and in vivo studies related to the effect of AEP on erosion concentrate on how the pellicle is able to protect the tooth. However, recent studies have shown how some proteins can interact, modulate the pellicle, and increase its protective effect against dental erosion.

Casein, for example, has been shown to have a considerable influence on the composition and formation of in situ salivary pellicle [Vacca Smith and Bowen, 2000]. When it was added to in vitro pellicle, Cheaib and Lussi [2011] showed that it had no impact on the protective function of the AEP. However, casein and mucin combined were able to significantly increase the efficacy of the pellicle against acid-induced enamel softening, indicating that protein cross-linking plays an important role in the effectiveness of the pellicle in preventing enamel erosion [Cheaib and Lussi, 2011]. In this regard, Rakhmatullina and coworkers [E. Rakhmatullina et al., unpubl. results] suggested that a complex between casein and mucin is formed, and the conformation of mucin is stabilized by casein. In other words, the addition of casein enhances the adsorption of mucin to the AEP, and this probably increases the protective effect of the AEP against erosion.

From a different perspective, the addition of casein to acid solutions and commercial soft drinks was able to considerably reduce in vitro enamel erosion [Hemingway et al., 2010]. The authors speculated that the casein added to the acid/soft drink can also interact with the AEP or with the enamel surface itself, resulting in a casein-rich film that may enhance protection against erosion [Hemingway et al., 2010]. Likewise, when casein was added

to a dentifrice together with other proteins, Jager et al. [2013] reported promising results for the prevention of erosion, but further research is still necessary to understand how and whether these products are able to prevent erosion *in vivo*.

Other inhibitors, such as condensed phosphates, and polyphosphates may all, to a certain degree, reduce the erosive potential of food and beverages [for a review, see Barbour and Lussi, 2014]. Mono-alkyl phosphates, which consist of an aliphatic organic chain esterified to a phosphate group, have shown a strong affinity to enamel, mediated by binding of the phosphate head group, and their protective effect of mineral dissolution seems to persist for several acid exposures [Jones et al., 2013, 2014]. However, their protection against erosion is, to some extent, limited because these compounds do not augment the protection of the salivary pellicle [Jones et al., 2013]. Since these compounds persist at the enamel surface despite repeated exposures to acid, they may offer valuable protection against dissolution of dental hard tissue during periods when the pellicle has been removed, e.g. by professional tooth cleaning or after consumption of an erosive product, by providing some protection for the enamel against subsequent acid impacts while the salivary pellicle is still reforming [Jones et al., 2014].

Some polymers, such as chitosan, have also been investigated. Chitosan is a natural polysaccharide derived from the deacetylation of chitin, found in the shells and exoskeleton of crustaceans [Illum, 1998]. In the pharmaceutical industry, it has been used as an excipient [Illum, 1998], but *in vitro* [Arnaud et al., 2010] and *in vivo* [Uysal et al., 2011] studies have shown some potential benefits in dentistry. It has been suggested that chitosan can form a layer-by-layer build-up on dental enamel, providing better protection against erosive attacks [Ganss et al., 2011]. This layer is formed because chitosan has a strong positive zeta potential, and it can readily adsorb to surfaces with a strong negative zeta potential [Claesson and Ninham, 1992], such as enamel [Young et al., 1997]. Chitosan was also shown to adsorb onto salivary pellicle proteins [Sano et al., 2001; van der Mei et al., 2007]. In the presence of mucin, both chitosan and mucin interact to form firmly attached multilayers [Dedinaite et al., 2005]. Furthermore, in combination with tin, the presence of chitosan promotes a significantly greater reduction of enamel loss both *in vitro* [Ganss et al., 2012; Carvalho and Lussi, 2014] and *in situ* [Schlueter et al., 2014]. It has been hypothesized that the chitosan could also shield the tin bound to the enamel,

thus enhancing the protection of the tin-rich layer and reducing the impact of the acids on the enamel (reducing microhardness loss) and, hence, reducing loss of tooth structure [Carvalho and Lussi, 2014]. Again, data on this subject is still scarce, and more *in situ/in vivo* studies should be carried out to fully elucidate the role of chitosan on erosion protection.

Conclusion

In spite of the increasing awareness of dental erosion among patients and dentists, there is still a need to improve the knowledge and attitudes related to this condition [Dugmore and Rock, 2003; Hermont et al., 2011; Skudutyte-Rysstad et al., 2013]. Although fluoride products are extensively recommended and widely used in oral health, fluoride formulations alone, used with the sole purpose of enhancing the formation of CaF_2 -like deposits, provide only limited protection against erosion [Hystad Hove et al., 2014]. This could explain the high prevalence of dental erosion still commonly found in various populations [Bartlett et al., 2013; Jaeggi and Lussi, 2014]. Thus, in order to accomplish optimal preventive procedures, it is necessary that erosion patients also make use of other protective agents. Furthermore, it should be borne in mind that the success of any protective agent is essentially rooted in further preventive measures. In other words, the causes of dental erosion should be meticulously investigated and dealt with, but for positive results from the use of any dental product to be obtained, the patients must rigorously comply with all additional preventive actions proposed by the dentists. On this note, we conclude that the future of fluoride alone in erosion prevention looks rather grim, but the combination of fluoride with other protective agents, such as polyvalent metal ions and some polymers, has much brighter prospects.

Disclosure Statement

The authors declare to have no conflict of interest.

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